CASWELL FILE 2-12-93

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

010031

FEB 12 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Brodifacoum Acute Dermal LD50 Study in Rats

TO: Rubis/Briscoe, PM 51
SRRD (H7508W)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 2/8/93
Toxicology Branch 2
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 2/8/93
Section Head, Review Section II
Toxicology Branch 2
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch 2 Marcia van Gemert 2/8/93
HED (H7509C)

DP Barcode: D178011 Submission: S417477

Chemical: 112701, Brodifacoum

Action Requested:

Review of MRID 422321-01 for Guideline 81-2

Comments and Recommendations:

1. The test material was applied in suspensions containing 1, 10, or 500 mg/kg technical (95.6%) brodifacoum, with 24-hr occluded dermal exposure, to groups of 5 male and 5 female rats. There was complete mortality at 500 mg/kg, and nearly complete mortality at 10 mg/kg (4/5 males and 5/5 females died or were sacrificed in extremis). Deaths occurred 5 to 11 days after exposure, and were attributable to internal hemorrhage. There were no mortalities at 1 mg/kg.

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2. The dermal LD50 values obtained were 5.21 mg/kg (males) and 3.16 mg/kg (females) for the 95.6% technical.

3. While the study is classified as core minimum data, it is not acceptable in satisfying guideline requirement 81-2 for the 0.25% (or whatever percentage is the highest registered in this country) brodifacoum-containing product that is used for manufacturing end-use products in this country. Refer to the memorandum dated February 18, 1992 (attached).

4. A copy of this memorandum and review should be provided to the registrant.

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 2/8/93
Section 2, Tox. Branch 2 (TS-769C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 2/8/93
Section 2, Tox. Branch 2 (TS-769C)

DATA EVALUATION REPORT I

STUDY TYPE: Acute Dermal LD50 - rat TOX CHEM NO. 112701

MRID NO: 422321-01

TEST MATERIAL: Brodifacoum

SYNONYMS:

STUDY NUMBER(S): CR2899; Report No. CTL/P/3595

SPONSOR: ICI Americas Inc.
Agricultural Products
Wilmington, DE 19897

TESTING FACILITY: ICI Central Toxicology Laboratory
Alderley Park, Macclesfield
Cheshire, UK

TITLE OF REPORT: Brodifacoum Technical: Acute Dermal Toxicity to the Rat

AUTHOR(S): McCall, J. C. & Leah, A. M.

STUDY COMPLETION DATE: December 20, 1991

CLASSIFICATION: Core Minimum Data. This study defines a dermal LD50 of 5.21 mg/kg (male rats) and 3.16 mg/kg (female rats) for material containing 95.6% brodifacoum, which is in toxicity category I in terms of its dermal toxicity hazard potential. This study is acceptable in fulfilling guideline requirement 81-2 and can be used to support the registration and/or reregistration of products containing approximately 95.6% brodifacoum. However, because of uncertainties in extrapolating the dermal LD50 value to the 0.25% formulating-use only product, this study cannot be used as supporting data for products containing 0.25% brodifacoum.

CONCLUSIONS:

1. The test material was applied in suspensions containing 1, 10, or 500 mg/kg technical brodifacoum, with 24-hour occluded dermal exposure, to groups of 5 male and 5 female rats. There was complete mortality at 500 mg/kg, and nearly complete mortality at 10 mg/kg (4/5 males and 5/5 females died or were killed in extremis). Deaths occurred 5 to 11 days after exposure, and were attributable to internal hemorrhage.

2. The dermal LD50 values obtained were 5.21 mg/kg (males) and 3.16 mg/kg (females) for the 95.6% technical. The test material is in toxicity category I in terms of its dermal toxicity (LD50) potential.

A. MATERIALS:

1. Test compound: Described (p. 10) as an off-white powder, sent from Sorex Ltd., Widnes, UK. "A certificate of analysis... supplied by Sorex stated that the sample had a purity of 95.6%. For the dose levels of 10 and 500 mg/kg the test sample was mixed to a paste with olive oil or corn oil respectively. For the dose level of 1 mg/kg, the test sample was formulated in polyethylene glycol 600 (PEG 600) to ensure accuracy of dosing."

2. Test animals: "Wistar-derived albino rats [Crl:(WI)BR strain) were supplied by Charles River Limited, Manston Road, Margate, Kent, UK. The rats were young adults and at the beginning of the study the males weighed 260-358 g and females weighed 179-233 g.

B. STUDY DESIGN:

1. Dose level selection: From p. 11: "The main study was preceded by a preliminary study (speculative dermal study) in which a range of dose-levels was tested on small groups of animals. Based on information from this study the initial dose-level for the main study was selected as 500 mg/kg. Additional dose levels of 1 and 10 mg/kg were added in order to assess the pattern of mortality."

2. Test material application: "For the dose level of 1 mg/kg, the test sample was formulated in PEG 600 and was spread evenly onto the shorn backs of the animals using a 1 ml sterile disposable plastic syringe; a volume of 2 ml/kg was applied. For the dose levels of 10 and 500 mg/kg, the appropriate amount of the test sample was weighed out...and made into a paste by adding a small amount (0.1-0.3 ml) of olive oil (10 mg/kg) or corn oil (500 mg/kg). Differences in dose level were achieved by altering the

amount applied to each rat. The amount applied was calculated for each animal according to its weight at the time of dosing. The test sample, covered by a gauze patch...was applied to the shorn backs of the animals and was kept in contact with the skin for approximately 24 hours using occlusive dressings..."

3. Statistics: "The acute dermal median lethal dose was calculated from the mortality data (the mortality data included animals that were killed in extremis) by logistic regression for the males, and was estimated using linear log-dose interpolation for the females, using nominal dose values. Confidence limits for the males were calculated using a likelihood ratio interval... and approximate confidence limits for the females are given by the highest dose with no mortalities and the lowest dose with 100% mortality. Dose-response curves are not given, as the slope could not be estimated."

4. There is a signed and dated "Statement of GLP Compliance" on p. 3 of the report. It includes the statement: "the investigations described in this report were conducted in accordance with the following Good Laboratory Practice standards, except
   (i) the stability of the test substance has not been reported.
   (ii) there is no documentation to indicate that the test substance characterisation was performed in a GLP-accredited Laboratory.
   (iii) the stability, homogeneity and achieved concentration of the test substance in the vehicle used were not determined by analysis."

C. METHODS AND RESULTS:

1. Observations: From p. 13: "Following a single dermal application of 1 mg/kg, there were no significant signs of toxicity or skin irritation in any animal..."

"Following a single dermal application of 10 mg/kg, four males were found dead or were killed in extremis between days 7 and 11 and all the females were killed in extremis between days 6 and 8. One of the males had a large open wound around its neck, which was caused by the collar. Due to the anticoagulant effect of the test sample, it was considered unlikely that the wound would heal, and the animal was therefore killed. The other animals which died or were killed showed signs of extreme toxicity (e.g. pallor, bleeding/bruising, breathing abnormalities) immediately prior to death, but had previously shown only minor abnormalities. There were no significant signs of toxicity in the surviving male. There were practically no signs of skin irritation in any of the animals."

"Following a single dermal application of 500 mg/kg, all the males were killed in extremis on days 5 or 6, and all the females were killed in extremis between days 5 and 8. All showed

signs of extreme toxicity similar to those seen at 10 mg/kg, and again had previously shown only minor abnormalities. There were practically no signs of skin irritation in any of the animals."

2. Necropsy findings: "The major findings in the animals which died or were killed in extremis were widespread hemorrhage, involving a variety of tissues and organs such as salivary gland and brain, but more especially involving the subcutis, thorax and thymus, causing discoloration and enlargement of the latter (in one instance the enlargement was described as a mass). Discoloration of bowel contents, epididymis, lung, pancreas and liver was also observed. A small number of organs was pale, possibly due to the lack of blood stasis after death."

3. Dermal LD50 values: From p. 15: "The acute oral (note: this word should be "dermal") of brodifacoum technical was calculated to be 5.21 mg/kg (95% confidence limits 1.95, 13.8) for the males, and was estimated to be 3.16 mg/kg (approximate confidence limits 1.00, 10.0) for the females."

D. DISCUSSION:

The study adequately demonstrates that test material containing 95.6% brodifacoum is in category I in terms of its dermal toxicity potential (dermal LD50 up to and including 200 mg/kg). It is noted that what was tested at the 1 mg/kg dose level was a suspension which included polyethylene glycol (and the dosage of this suspension was essentially 2 ml/kg; the density of PEG 600 is 1.126 gm/ml, so what was tested was 2.25 gm/kg of a "dosing mixture" containing 0.044% technical brodifacoum; since the technical brodifacoum was 95.6% active the formulation contained 0.0425% active). Normally, we would accept a dermal LD50 study only if the test material had been moistened with minimal amounts of water or physiological saline, sufficient to make a paste; however, since the results of this study demonstrate that the test material is in toxicity category I, we can accept the study and its findings.

Because of uncertainties in extrapolating the dermal LD50 value to the 0.25% formulating-use only product, this study cannot be used as supporting data for products containing 0.25% brodifacoum. According to a memorandum dated February 18, 1992 (see attachment) a "technical" brodifacoum containing something like 90-100% active is not sold in the United States. Instead, there is a "concentrate" containing 0.25% active ingredient, and this is what is used to formulate end-use products (which usually contain 0.005% active). The battery of acute toxicity studies normally conducted on a technical should be done on the 0.25% concentrate (or that registered product having the highest percentage of active ingredient) used for manufacturing end-use products.

~~SECTION HEAD~~
COPY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 18 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Acute Data for Brodifacoum

TO: Rubis/Briscoe, PM 51
SRRD (H7508W)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 1/27/92
Toxicology Branch 2
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 1/28/92
Section Head, Review Section 2
Toxicology Branch 2
HED (H7509C)

and

Marcia van Gemert 2/7/92
Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch 2
HED (H7509C)

DP Barcode D172556 Case 816404

Project No. 2-0875

Tox. Chem. 114AAA

Action Requested:

This submission from ICI Agricultural Products states that there have been problems in the acute testing of this compound involving 1) its high toxicity, particularly to rodent species (understandable, as the compound is a rodenticide) and 2) laws in the United Kingdom relating to the testing of highly toxic compounds in laboratory animals. "Due to the technical difficulties encountered in both the acute oral and acute dermal studies...ICI has been unable to progress along the stepwise pathway beyond these studies and therefore has not been able to fully comply to the agency's request for acute eye and dermal irritation studies."

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Comments and recommendations:

1. The information the Agency has available indicates that a "technical" for Brodifacoum containing something like 90-100% active ingredient is not sold in this country. Instead, there is a "concentrate" containing 0.25% active ingredient, and this is what is used to formulate end-use products (which generally contain 0.005% active).

2. The battery of acute toxicity studies (oral LD50, dermal LD50, primary dermal and eye irritation, dermal sensitization) should be done on the 0.25% concentrate used for manufacturing end-use products (or that registered product having the highest percentage content of active ingredient). According to the one-liners (see attached copy) a number of acute studies (including a dermal sensitization study) on a 0.25% Brodifacoum-containing formulation have been received and reviewed. We are uncertain whether these studies would satisfy all or even some of the acute toxicity data requirements. If the registrant wishes to cite these studies to satisfy this set of data requirements, the studies will have to be re-reviewed in order to determine whether they are acceptable by today's standards.

3. Because of the toxicity of Brodifacoum, HED recommends that this chemical be placed in special review.